REMARKS

I. Status of the Claims

Claim 17 has been canceled and new claims 19-32 have been added.

II. The Present Amendment

No new matter has been added by the present amendment.

The title has been amended to reflect the claims pending after entry of the present amendment.

New claims 19-22 are drawn to isolated, full-length mesothelin (SEQ ID NO:2), to proteins with at least 90% sequence identity to SEQ ID NO:2, to isolated peptides of at least 10 contiguous amino acids of SEQ ID NO:2, and to isolated peptides having at least 90% sequence identity to stretches of contiguous amino acids of SEQ ID NO:2. The claims are supported throughout the specification. The discovery of full-length mesothelin is described, for example, on page 8, line 21, to page 9 line 6. Peptides of at least 10 contiguous amino acids of SEQ ID NO:2 are supported by, for example, page 15, lines 1-16. Recitations regarding peptides and proteins with at least 90% sequence identity to mesothelin are supported throughout the specification, including page 15, lines 1-14 (referring to portions of mesothelin which can be used as immunogens), page 46, lines 24-37 (which indicates that conservative substitutions can be made in the amino acid sequence for mesothelin without affecting biological activity) and page 6, lines 19-30 (referring to determining sequence identities of peptides). Recitations regarding use of mesothelin or peptides thereof to raise antibodies are supported throughout the specification, including page 14, line 26, to page 17, line 33. Recitations regarding the recognition of mesothelin, peptides thereof, or proteins or peptides with substitutions of the mesothelin sequence by T cells from patients with mesothelin-expressing cancers is supported throughout the specification, including page 46, line 22, to page 47, line 17.

Compositions comprising mesothelin or portions thereof in pharmaceutically acceptable carriers are likewise supported throughout the specification.

For example, the combination of an antigen with a pharmaceutically acceptable carrier is supported throughout the specification, including page 46, lines 17-20. The use of adjuvants in combination with an antigen in a pharmaceutically acceptable carrier is supported throughout the specification, including page 45, lines 11-30. The conjugation of a peptide to a carrier is supported throughout the specification, including page 44, line 29 to page 45, line 10. The recitation that a portion of mesothelin employed as an antigen comprises at least 10 contiguous amino acids of the full length sequence is supported throughout the specification, including page 9, lines 7-12 and page 15, lines 1-14. See, e.g., page 46, lines 24-37.

III. The Office Action

The Action rejects claim 17 on several grounds. The rejections posed by the Action will be considered in turn.

A. Rejections Under 35 U.S.C. § 112, second paragraph

1. Rejection over whether claim reads on composition or method

Claim 17 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. According to the Action, the claim is drawn to a vaccine, but uses terminology suggesting a method. The Action therefore assets that it is unclear whether the claim is drawn to a composition or to a method of treatment.

While not necessarily agreeing with the Action, the claim has been canceled. The claims introduced in the present Amendment are drawn to compositions, not methods.

2. Rejection regarding mesothelin-derived antigen

The Action further rejects claim 17 under § 112, second paragraph, on the ground that the scope of what would be considered a mesothelin-derived antigen is unclear. The Applicants do not necessarily agree with the Action. To expedite prosecution, however, the new claims are drawn either to full length mesothelin, to

proteins that have at least 90% sequence identity to SEQ ID NO:2 and which, when used as an immunogen, raise antibodies which recognize full-length mesothelin (SEQ ID NO:2) or activate T-cells to recognize mesothelioma or ovarian cancer cells expressing mesothelin, to peptides of at least 10 contiguous amino acids of SEQ ID NO:2, or to peptides of at least 10 amino acids that have at least 90% sequence identity to a stretch of at least 10 contiguous amino acids of SEQ ID NO:2 and which, when used as an immunogen, raise antibodies which recognize full-length mesothelin (SEQ ID NO:2) or activate T-cells to recognize mesothelioma or ovarian cancer cells expressing mesothelin. Thus, the new claims drawn to the proteins and peptides contain both structural and functional recitations. Applicants respectfully submit that the new claims are therefore free of the indefiniteness rejection asserted by the Action with respect to claim 17.

B. Rejection Under 35 U.S.C. § 112, first paragraph

The Action further rejects claim 17 under 35 U.S.C. 112, first paragraph. According to the Action, claim 17 is rejected as drawn to subject matter which was not described in such as way as to enable a person of skill in the art to make and use the invention. The Action characterizes the claim as drawn to the "extremely complex and unpredictable field of cancer vaccines and in vivo cancer treatment." Action, at page 3. The Action then follows that statement with a series of contentions. Applicants amend in part and traverse in part. For clarity, Applicants have attempted to separate out the various contentions and to address them individually below.

Before turning to the specific contentions set forth in the Action, Applicants note that the proteins and peptides of the claims as now pending, and the compositions of the proteins or peptides in pharmaceutically acceptable carriers, can be used, for example, in animals to raise polyclonal or monoclonal antibodies against mesothelin. See, e.g., specification at page 15, line 22, to page 16, line 36. Such antibodies can be used, for example, *in vitro* to detect the presence of mesothelin-expressing cells in a biological sample. See, e.g., specification at page 17, line 35 to page 19, line 12; page 47, lines 20-24. Further, the specification observes that mesothelin has

been discovered to be involved in cell adhesion and that antibodies to mesothelin (raised, for example, by administering the compositions of claims 19-32) would be useful in inhibiting the spread of ovarian cancer cells into the peritoneal wall. See, specification, at page 10, lines 20-32. The proteins, peptides, and pharmaceutical compositions comprising them are fully enabled on this basis alone. Applicants note, however, that the proteins, peptides, and compositions can also be used as immunogenic compositions to raise or to heighten an immune response in a person with a mesothelin-expressing cancer or in a person at risk of developing such a cancer.

1. Contention regarding difficulties of determining patients to receive a vaccine

The Action presents a group of arguments directed to the idea that it would be difficult to predict "populations which might be susceptible to specific cancers, such that appropriate patients would receive vaccines which recognized and prevented cancer which those patients might develop." Action, at page 3, bottom paragraph.

Applicants respectfully make three points in response. First, Applicants note that this cluster of contentions would be better directed to claims drawn to methods of treating persons at risk of developing a mesothelin-expressing cancer. The present claims, however, are drawn simply to proteins, peptides, and compositions comprising the proteins and peptides, not to methods.

Second, the Action's contentions speak to the alleged difficulties of determining who might develop cancer in the future. The contentions therefore are not applicable to compositions given to induce or to heighten an immune response to an already existing cancer. Thus, the contentions are not well founded since the compositions of the invention can be administered to raise antibodies or to activate T cells against existing mesothelin-expressing cancers, such as mesotheliomas and mesothelin-expressing ovarian cancers.

Third, the difficulties the Action perceives in general in selecting appropriate populations which might be appropriate candidates for a cancer vaccine may

be true for cancers in general, but are not present with regard to some subsets of mesothelin-expressing cancers. In this regard, the specification notes that one of the cancers that expresses mesothelin is mesothelioma. E.g., page 8, lines 21-24. The great majority, 80%, of persons presenting with mesothelioma have had exposure to asbestos, (e.g., Sugarbaker et al., *Cancer Control*, 4(4) (July 1997) (citing the 80% figure; a copy of the on-line version of this peer-reviewed publication is attached for the Examiner's convenience), and several hundred thousand people are currently suing asbestos manufacturers not because they are sick, but because they are afraid of developing an asbestos-caused cancer in the future. A website by the Asbestos Alliance, devoted to litigation related to asbestos indicates, in a section entitled "The Scope of the Asbestos Litigation Problem" that some 200,000 some asbestos related claims are now pending, largely by people who are not yet sick. (A copy of the relevant page of the website is provided for the Examiner's convenience. Applicants believe that the problem regarding the number of asbestos-related cases, and the assertion that the plaintiffs are at increased risk of mesothelioma, are so well known that the Office can take notice thereof; they will, however, introduce more evidence on this point if the Examiner so requests). The persons bringing these suits assert that they are at risk for developing mesothelioma, and therefore provide a self-selected population of candidates for immunogenic compositions to heighten their immune response to mesothelin-expressing cancers. Accordingly, the problems the Action argues are generally present in identifying persons at risk for developing a particular cancer are simply not present with respect to at least some of the potential candidates for immunogenic compositions against mesothelioma.

2. Contention that "Methods" and Compositions of the Invention have to Prevent Cancer

The Action further contends, at the top of page 4, that "in order to prevent cancer, a method would necessarily have to anticipate the cancer which the patient would develop, and be sufficiently immunogenic to prevent that cancer." The Action further alleges, in the same vein, that "the goal of tumor vaccination is to prevent tumor

recurrence and to eliminate residual disease." Page 4, second paragraph. These statements demonstrate that the Action is applying an improper standard.

As an initial matter, the Action's statements regarding requirements pertaining to methods for anticipating cancer are presumably related to the alleged indefiniteness of claim 17, which was asserted to refer to both a method and to a composition. The instant claims are drawn to compositions, not methods. Therefore, to the extent the rejection is drawn to concerns regarding the need for a method to anticipate the cancer a patient would develop, it is not pertinent to the examination of the present claims.

Assuming for the sake of argument that the Action's contention has some application to the present claims, which Applicants do not concede, Applicants note that there are classes of persons who would clearly benefit from the administration of compositions of the invention. As set forth in the preceding section, there are hundreds of thousands of people who have identified themselves as at risk for developing a mesothelin-expressing cancer and who are seeking damages in court for the fear they will develop mesothelioma in the future. These persons are candidates for compositions to increase their immune response to mesothelioma cells.[1] Likewise, there are guidelines for determining persons at higher risk of developing ovarian cancer. And, of course, persons already diagnosed with mesothelioma or with ovarian cancer are candidates for administration of mesothelin or a protein or peptide that raises antibodies that recognize mesothelin or that activates T cells that recognize mesothelin, to enhance their immune response to the cancer.

Thus, the difficulties hypothesized by the Action in determining who might be a suitable candidate for administration of the claimed compositions are simply

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[1] The specification does not necessarily identify persons in fear of developing mesothelioma as potential beneficiaries of the vaccine embodiments. The asbestos litigation crisis has been in progress for some 20 years (see, e.g., the excerpt from the Asbestos Alliance website attached hereto), and are well known to the public at large. Applicants respectfully submit that persons of skill in the art could hardly fail to note persons exposed to asbestos as a potential candidate group for a heightened immune response to mesothelin. The Examiner is respectfully reminded that the application does not need to teach that which is

not present with respect to the proteins, peptides, and compositions comprising the proteins or peptides now claimed. Finally, even assuming that some additional persons who could benefit from heightened immune response to mesothelin cannot be determined, that would be irrelevant to the examination of the present claims. Applicants are aware of no provision in the patent laws that requires a composition claim to be supported by identifying all persons who might benefit from its administration.

3. Contention Regarding Guessing Which Antigens Need To Be Protected Against

The Action further alleges that "guessing which antigens need to be protected against is well outside of the realm of routine experimentation." Action, at page 4, top paragraph.

The point of this comment is unclear. One does not protect against "antigens" but rather against cells bearing antigens expressed on cancer cells but not normal cells, or overexpressed on cancer cells compared to normal cells. The present specification identifies mesothelin as an antigen expressed or overexpressed on cells of particular cancers. The specification has therefore already identified the conditions to be protected against, and an antigen that can be used to provide the protection. No guessing by the practitioner is required. Additionally, the specification observes that mesothelin has been discovered to be involved in cell adhesion and that antibodies to mesothelin would be useful in inhibiting the spread of ovarian cancer cells into the peritoneal wall. See, specification, at page 10, lines 20-32. Therefore, no undue experimentation by the practitioner is required to practice the invention as claimed.

Applicants respectfully remind the Examiner that, even if some experimentation is required to determine whether any particular antigen within the scope of the claims provokes an immune response, that does not affect the enablement of the invention. The question is not whether some experimentation is necessary, but whether

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well known to persons of skill in the art. *See, e.g.*, MPEP § 2164.01, *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986).

the experimentation required is "undue." The specification notes that epitopes on mesothelin can be mapped to identify particularly strong epitopes. Specification at, e.g., page 46, line 22, to page 47, line 17, and mapping and testing of the immunogenicity of epitopes is routine in the art. MPEP § 2164.01 states: "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." No undue experimentation is required to practice the invention as claimed.

4. Contention that the Goal Of Tumor Vaccination is To Prevent Tumor Recurrence or to Eliminate Residual Disease

The Action next contends that the "the goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease," Action at page 4, bottom paragraph, and cites Ezzell, J. NIH Res., 7:46 (1995) for the proposition that "no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy." *Id.* Applicants traverse.

The Action rejects claim 17 on a false ground. Claim 17 as presented did not recite the prevention of tumor recurrence, the elimination of residual disease, or the curing of cancer. Claim 17 is drawn to a vaccine for the inhibition of mesotheliomas or ovarian cancers. Applicants respectfully observe that increasing a patient's immune response to their cancer slows the growth of that cancer and benefits the patient whether or not the cancer is whether or not tumor recurrence is fully blocked or residual disease is fully stopped. There is no requirement in the patent laws that a vaccine cure a disease to be useful or enabled.

To clarify this issue, claim 17 has been canceled and new claims introduced to proteins, peptides, and compositions of these proteins and peptides in pharmaceutically acceptable carriers. Such compositions can, for example, be administered to animals to raise antibodies to mesothelin. As pointed out above, they are

thus fully enabled on this basis alone, even though they can also be administered to patients to induce or to heighten an immune response to mesothelin-expressing cancers.

5. Contentions that Cancer Vaccines Do Not Work And Must Replace Standard Therapeutic Strategies

On the bottom of page 4 of the Action, the Action cites an editorial by Spittler, Cancer Biotherapy, 10:1-3 (1995) (hereafter, "Spittler") and states that Spittler " recognizes the unpredictability of the nature of the art when she states that 'Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: 'cancer vaccines don't work." On page 5 of the Action, the Action contends that "the goal of most vaccines is therapeutic efficacy . . . [Evans and Kaye, Q J Med 92:299-307 (1999) (hereafter, "Evans and Kaye")] conclude that (page 303, last column) – [] the notion that cancer vaccines will replace standard therapeutic strategies in malignant disease still belongs in the realm of fiction."

This section of the Action's contentions suffers from several flaws, each of them fatal. First, claim 17 as presented did not contain a recitation which requires that the compositions of the invention must replace standard therapies. Thus, the Action improperly imports into the claim a limitation it does not recite, and then inappropriately rejects the claim for allegedly not enabling the imported, but unrecited, limitation.

Second, a more complete reading of Spittler reveals that the characterization of the positions of oncologists and pharmaceutical executives set forth at the beginning of the editorial[2] indicates that those positions are based on the fact that, until the late 1980's and early 1990's, cancer vaccines were based on whole tumor cells. Spittler, at page 1, left and right columns, bridging paragraph. On page 2, Spittler notes that the experience is different with cancer vaccines based on the newer discovery of tumor associated antigens. In this regard, Spittler states: "Almost everyone working in

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[2] The "quotations" set forth in the introduction of Spittler's editorial are not actual statements by real individuals, rather, they are mere hypothetical statements alleged to characterize the then-current views of clinicians and executives of large pharmaceutical companies.

this field has had the experience of seeing a dramatic regression of metastatic disease following vaccine therapy," (Spittler, at page 2, left column), and cites no fewer than 7 groups that have "reported clinical successes with vaccine therapy in large series of patients." *Id.* at page 2, right column.[3]

Third, the very paragraph of Evans and Kaye which ends with the language quoted by the Examiner *against* the enablement of claim 17 (that "the notion that cancer vaccines will replace standard therapeutic strategies in malignant disease still belongs in the realm of fiction"), commences with the statement "The notion that the immune system can be activated by cancer vaccines to attack and reject established tumors is a fact." (Emphasis added.) Thus, the reference cited by the Action *against* claim 17 unequivocally supports it. The reference states that cancer vaccines activate the immune system to attack tumors. Activating the immune system is what vaccines are intended to do, and the very reference cited by the Action against claim 17 therefore supports, rather than undercuts, its enablement. Applicants respectfully observe that it is impermissible for the Action to focus on one portion of a reference that allegedly undercuts enablement while at the same time ignoring portions of the same reference that support it. Applicants also respectfully observe that there is no requirement in the patent law that an claimed invention has to replace current standard therapies to be useful or to be enabled.

In sum, the references cited by the Examiner do not support the thesis that claim 17 is not enabled. To expedite prosecution, however, claim 17 has been canceled and new claims introduced. The new claims are enabled by, among other things, their utility in raising anti-mesothelin antibodies. This enablement is not removed simply because the claimed proteins, peptides, and compositions are also useful when administered to raise or to heighten an immune response to a mesothelin-expressing

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[3] Spittler also states that there are a number of negative studies in the literature. But her only citation on this point is a 1991 text on cancer "biotherapy." Relatively few cancer antigens had been identified, cloned and sequenced by that time, so it is likely the studies referred to in this text were of antigens isolated from lysed cells or released from cells by proteolytic processes that altered their

cancer. Thus, Applicants state for the record that the new claims do not narrow any element of claim 17 as presented; they are, accordingly, entitled to the full range of equivalents for every element of claim 17 as originally presented, and of the claims as presented in this Amendment.

IV. Filing Receipt

On February 20, 2001, Applicants requested that the filing receipt regarding this application be corrected to state the correct number of the PCT application of which this application is a national stage filing, and to add a reference to the provisional application from which priority is claimed. Neither error was corrected. Applicants enclose herewith a further copy of the filing receipt with the requested corrections and ask the Examiner's help in seeing that the corrections are made.

V. Information Disclosure Statement

Applicants note that the Action did not include an initialed copy of the Information Disclosure Statement (IDS) filed with the application. Applicants respectfully request that the Examiner return a copy of the IDS, initialed to show the Examiner's consideration of the references, along with the next official action.

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immunogenicity. The mesothelin of the subject application, by contrast, was cloned and expressed recombinantly,

PATENT

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,

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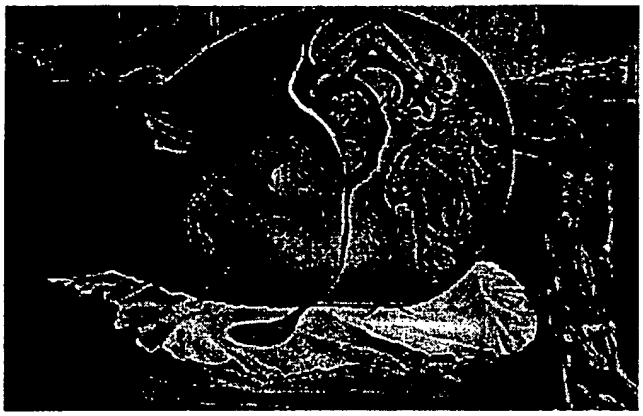
Enclosures: Sugarbaker et al.
Asbestos Alliance webpage
Filing receipt showing corrections

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the title:

MESOTHELIN, IMMUNOGENIC PEPTIDES DERIVED THEREFROM, AND COMPOSITIONS COMPRISING MESOTHELIN OR IMMUNOGENIC PEPTIDES THEREOF [, A DIFFERENTIATION ANTIGEN PRESENT ON MESOTHELIUM, MESOTHELIOMAS AND OVARIAN CANCERS AND METHODS AND KITS FOR TARGETING THE ANTIGEN]



Salvador Dali (Spanish, 1904-89).
Geopoliticus Child Watching the Birth of the New Man (1943).
Oil on canvas, 18 x 20-1/2 inches. Collection of the Salvador Dali Museum, St. Petersburg, Florida.

Current Therapy for Mesothelioma

David J. Sugarbaker, MD, Jose J. Norberto, MD, and Raphael Bueno, MD

Malignant pleural mesotheliomas are locally aggressive, invasive, and almost universally fatal.

Background: *Diffuse malignant pleural mesotheliomas (DMPMs) are highly lethal tumors that are becoming more common. Standard management approaches have provided limited effectiveness.*
Methods: *The literature on management has been revised, and the authors present their data on outcomes for 120 patients treated with an aggressive trimodality approach.*
Results: *An aggressive trimodality approach including extrapleural pneumonectomy followed by chemoradiation produces low mortality and acceptable morbidity. The five-year survival rate in patients with epithelial histology and negative nodes approaches 40%.*
Conclusions: *Nodal status and histologic subtype are major predictors for survival in patients with early DMPM. A uniformly accepted staging system would allow comparison of treatment approaches from various institutions. More effective management interventions are required.*

Introduction

Mesotheliomas of the pleural cavity are relatively rare tumors. Generally, two types of pleural tumors can be referred to as mesotheliomas. The less common is the solitary (or localized) fibrous tumor of the pleura, previously known as "benign mesothelioma." This slow-growing, commonly benign, well-circumscribed tumor is pedunculated on a pleural-based pedicle and often is cured by resection. The tumor appears to originate from submesothelial rather than mesothelial or epithelial cells.[1] The more

common variety is the diffuse malignant pleural mesothelioma (DMPM), a true mesothelial malignancy that is locally aggressive, invasive, and almost universally fatal. This multicentric tumor infiltrates the pleural space, results in a pleural effusion, and mechanically compresses the surrounding structures. Though distant metastatic lesions may be seen in up to 30% of cases in autopsy series, most patients die of locoregional invasion and compression of vital structures. The median survival for patients with DMPM is between four and 12 months, depending on the stage at presentation.

Etiology

Asbestos exposure is the best known and most common risk factor associated with DMPM.[2] Asbestos has commonly been used for insulation, and it also has been used in the shipbuilding industry and in construction. The amphibole type of asbestos is inhaled and collected in the peripheral alveoli during unprotected exposure. It eventually erodes and reaches the subpleural space where it continuously stimulates inflammation and carcinogenesis.[2] However, a history of asbestos exposure is elicited in only 80% of patients who present with mesothelioma. Other factors that may promote DMPM include chronic lung infections, tuberculous pleuritis, radiation, and some mineral fibers.[2,3] The simian virus 40 (SV40) has been implicated as a potential etiologic factor after sequences corresponding to its T antigens were isolated from human samples of diffuse malignant mesothelioma but not from adjacent normal lung.[4,5] Furthermore, tumors histologically identical to malignant mesothelioma have developed when SV40 DNA material is injected into the pleural cavities of hamsters.[6] Cigarette smoking does not appear to be related to the development of mesothelioma, although the relationship among smoking, asbestos exposure, and lung cancer is clear.

Epidemiology

In the United States, 2,000 to 3,000 patients are diagnosed with DMPM each year, representing a 50% increase in the number of cases over the last decade. This increase probably reflects the long latency period between the asbestos exposure in the 1940s to 1960s and the clinical manifestation of DMPM.[79] The appearance of a new etiologic factor (eg, SV40-contaminated polio vaccines) is also a possible reason for the increase. Women are less likely to be affected than men, possibly due to womenís scarce asbestos exposure resulting from different employment patterns. The disease is most common in the sixth decade of life.

Presentation and Diagnosis

The majority of the patients (60% to 90%) present with dyspnea and chest discomfort.[3] The dyspnea is usually caused by an expanding pleural effusion that eventually becomes loculated. Inevitably, the pleural space fills with tumor that invades and compresses all the adjacent structures and thus limits lung expansion. The chest discomfort is usually dull and nonspecific at presentation. Once the chest wall and intercostal nerves are invaded by tumor, the pain is more localized and severe, which indicates advanced disease. Less common symptoms include fever, night sweats, cough, malaise, and weight loss.

In cases of advanced disease, the patient may present with ascites, cachexia, or chest and abdominal wall deformity. Thrombocytosis is a relatively common finding and may be associated with a poorer prognosis.[10] Other associated paraneoplastic abnormalities include hypoglycemia, hypercalcemia, thrombocytosis, pulmonary embolism, autoimmune hemolytic anemia, hypercoagulability, and syndrome of inappropriate secretion of antidiuretic hormone (SIADH). These complications are

extremely rare.

Physical examination reveals diminished breath sounds on the affected side due to the effusion and atelectasis. In advanced disease, palpation of a chest wall mass is an indication of thoracic wall invasion. Abdominal fullness also may be present. Such transdiaphragmatic invasion often results in ascites and renders the tumor unresectable. Bowel obstruction is observed in 30% of the patients once transdiaphragmatic invasion has occurred.

A thorough radiologic evaluation is performed to determine the stage of tumor and to help in the design of therapy. Posteroanterior and lateral chest radiograph, computed axial tomography scan of the chest and upper abdomen and, in some centers, magnetic resonance imaging (MRI) of the chest constitute the requisite staging and evaluation. The chest radiograph typically reveals a pleural effusion with or without pleural calcifications. In our institution, we routinely obtain a computed tomography scan and MRI of the chest and upper abdomen. These studies allow greater accuracy in determining whether tumor has surpassed the confines of the ipsilateral pleural space.[11] Radiologic criteria of unresectability include invasion of mediastinal structures, transdiaphragmatic involvement, and metastatic disease. Examination of the sagittal sections of the involved chest by MRI allows for a sensitive determination of mediastinal and diaphragmatic invasion.

We have also found two-dimensional echocardiography (2D ECHO) to be useful in searching for pericardial effusions and tumor infiltration through the pericardium. This modality is also helpful in determining whether the patientís baseline myocardial function and pulmonary artery pressure will allow an aggressive resection.

The pleural effusion may be examined via thoracentesis. The pleural effusion associated with mesothelioma is usually yellow and thus different from the blood-containing effusion that is characteristic of adenocarcinoma. A diagnosis of DMPM is rarely possible by cytology because malignant cells are seldom seen in these effusions; when they are present, it is often difficult to correctly identify the malignancy. Therefore, to establish a definite diagnosis, it is usually necessary to perform a pleural biopsy. The closed pleural biopsy, widely used in the past, is helpful only when the results are positive. Negative pleural biopsies should be interpreted with caution and, if clinically suspicious, should be followed by open biopsies. Thoracoscopy or pleuroscopy, therefore, is the best approach to obtain pleural tissues in patients with suspected mesothelioma. In this manner, generous biopsies of the involved areas in the pleura are obtained, and frozen section analysis can confirm that the material is sufficient for final diagnosis. Thoracentesis, pleuroscopy, and thoracoscopy should all be performed through strategically placed incisions because mesothelioma cells can easily seed the tracts of the incisions used for the diagnostic biopsy. We usually place one or, at most, two thoracoscopy ports on the patient's chest in an area that will be included in a subsequent resection. Planning avoids recurrence in the port sites. In cases of obliterated pleural space where a thoracoscope cannot be inserted, an open pleural biopsy is performed.

Pathogenesis and Histology

The earliest pathologic findings are small nodules that are present in parietal pleura. The tumor crosses the pleural space to involve the visceral pleura, coalesces, and replaces the pleural space. As the tumor mass becomes locally advanced, it constricts the underlying normal pulmonary parenchyma. Late in the disease process, the tumor invades the pericardium and mediastinum and may metastasize elsewhere. Patient death is usually caused by compression of the heart and the lung.

DMPM derives from mesothelial stem cells that are, by definition, pluripotential. The cells differentiate

into epithelial or mesenchymal elements. It is common to find both cell types in the same tumor specimen. The dominant histology classifies DMPM as having epithelial (50%), sarcomatous (35%), and mixed (15%) histologic groups. This histologic classification has prognostic implications. Several studies have demonstrated that epithelial-type mesothelioma has a better prognosis than the sarcomatous and mixed types.[12,13]

The histopathologic diagnosis of mesothelioma can be difficult. Common diagnostic dilemmas for the pathologist include differentiation between adenocarcinoma and tubulopapillary mesothelioma (Table 1),[14] between reactive mesothelial hyperplasia and early mesothelioma, and between desmoplastic mesothelioma and benign pleuritis or plaquing. Use of immunochemistry stains by an experienced pathologist who has access to sufficient fresh and formalin-fixed tissue will optimize results.

Table 1. – Diagnostic Aids to Differentiate Malignant Pleural Mesothelioma From Adenocarcinoma

	Malignant Mesothelioma	Adenocarcinoma
Histology		
Periodic acid-Schiff stain	negative	positive
Mucicarmine stain	negative	positive
Immunostaining		
Carcinoembryonic antigen	negative	positive (75%)
Leu-M1	negative	positive
Vimentin	positive	negative
Cytokeratin	positive	negative
Electron microscopy	long microvilli	short microvilli

From *Textbook of Surgery. The Biological Basis of Modern Surgical Practice.* 15th ed. Sabiston DC Jr, ed. WB Saunders Co: 1996. Reprinted with permission.[14]

the combination regimen.[19]

Staging Systems

DMPM appears to be a heterogeneous disease with different patient survival statistics reported by various authors. Characteristics such as young age, female gender, epithelial subtype, normal platelet count, uninvolved lymph nodes, and absence of pain have been associated with longer survival, but the lack of consensus on a uniform staging system prevents a valid comparison of patients from various institutions. An essential factor in any analysis of disease requires a solid staging scheme that allows the clinician to categorize patients in homogeneous groups with established survival curves to permit evaluation of therapy.

Several staging systems for DMPM have been presented. Developed in 1976, the Butchart staging system[15] was based on a series of 29 patients who were treated with extrapleural pneumonectomy (EPP). The four stages indicate tumor, lymph node location (either inside or outside of the chest), and blood-borne metastases. It does not address tumor burden. This scheme was used because of its simplicity, but the association of stage with survival was unclear, and the staging system is now obsolete.

Chahinian[16] was the first to apply the variables of tumor (T), lymph node (N), and metastasis (M) to DMPM staging in the early 1980s. However, this staging system does not correctly separate resectable and unresectable patients and is not useful in predicting patient survival. The major drawback with any TNM classification system in DMPM is the difficulty in quantifying the T stage, especially early in the

disease, in any surgically and prognostically meaningful terms.

A revised TNM staging scheme was proposed in 1990 by the International Union Against Cancer (UICC).[17] While the definitions of the T categories are more precise than those in the Chahinian system, the degree of tumor infiltration beyond the preresectional extension is not appropriately described. In a malignancy such as mesothelioma in which tumor usually spreads locally, the T category must account for the degree of tumor infiltration and for tumor resectability. In the UICC staging scheme, the T variable remains imprecise. The nodal scheme is also a potential pitfall. The same nodal designations used in the UICC lung cancer staging system are applied in this DMPM system. However, in reality, this tumor is more pleural than hilar, and it behaves differently from lung cancer in lymphatic drainage, thus making the nodal category (N) potentially unreliable. The application of the M category is of limited value because many patients die of persistent local disease. Thus, the UICC system has major limitations.

The most recent TNM-based system was created by the International Mesothelioma Interest Group (IMIG) in June 1994 at the Seventh World Conference of the International Association for the Study of Lung Cancer (Table 2).[18] By incorporating recent prognostic data on T and N status, the IMIG system provides both a more detailed description of the T status and a better delineation of subtle differences (eg, parietal vs visceral pleural involvement). It uses the same N and M categories as the lung cancer TNM-based system. This system, which has been validated on retrospective data, will probably require revision.

Table 2. – International Mesothelioma Interst Group Staging System for Diffuse Malignant Pleural Mesothelioma

T = tumor

T1a Tumor limited to the ipsilateral parietal pleura including mediastinal and diaphragmatic pleura. No involvement of the visceral pleura.

T1b Tumor involving the ipsilateral parietal pleura, including mediastinal and diaphragmatic pleura. Scattered foci of tumor also involving the visceral pleura.

T2 Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features:
- Involvement of diaphragmatic muscle
- confluent visceral pleural tumor (including the fissures) or extension of tumor from visceral pleura into the underlying pulmonary parenchyma

T3 Describes locally advanced but potentially resectable tumor. Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features:
- involvement of the endothoracic fascia
- extension into the mediastinal fat
- solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall
- nontransmural involvement of the pericardium

T4 Describes locally advanced technically unresectable tumor. Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral) with at least one of the following features:
- diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction
- direct transdiaphragmatic extension of tumor to the peritoneum
- direct extension of tumor to the contralateral pleura
- direct extension of tumor to one or more mediastinal organs
- direct extension of tumor into the spine
- tumor extending through to the internal surface of the pericardium with or without a pericardial effusion; or tumor involving the myocardium

N = lymph nodes

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastases
N1 Metastases in the ipsilateral bronchopulmonary or hilar lymph nodes
N2 Metastases in the subcarinal or ipsilateral mediastinal lymph nodes, including the ipsilateral internal mammary nodes
N3 Metastases in the contralateral mediastinal, contralateral internal mammary, ipsilateral, or contralateral supraclavicular lymph nodes

M = metastases

MX Presence of distant metastases cannot be assessed
M0 No distant metastasis
M1 Distant metastasis present

Stage:	Description:
Stage Ia	T1a N0 M0
Stage Ib	T1b N0 M0
Stage II	T2 N0 M0
Stage III	Any T3 M0 Any N1 M0 Any N2 M0
Stage IV	Any T4 Any N3 Any M1

From Rusch VW. A proposed new international TNM staging system for malignant pleural mesothelioma. *Chest.* 1995;108:1122-1128. Reprinted with permission."

The Brigham staging system was introduced after analyzing the first 52 patients treated with trimodality therapy at the Dana-Farber Cancer Institute/Brigham and Women's Hospital Thoracic Oncology Program.[12] This staging scheme allows four stages and considers resectability and nodal status (Table 3). Patients with stage I disease have resectable tumors with no affected lymph nodes. Stage II refers to resectable tumors accompanied by positive lymph nodes. Stage III includes tumors that are unresectable due to local extension into mediastinal structures or through the confines of the diaphragm. Stage IV describes metastatic disease at presentation. Fig 1 demonstrates the Kaplan-Meier curves in which survival of 120 patients was stratified according to stage.[13] (PLEASE SEE HARD COPY OF JOURNAL FOR FIG 1.)

Table 3. – Brigham Staging System for Malignant Pleural Mesothelioma

Stage	Definition
I	Disease confined to within capsule of the parietal pleura: ipsilateral pleura, lung, pericardium, diaphragm, or chest-wall disease limited to previous biopsy sites
II	All of stage I with positive intrathoracic (N1 or N2) lymph nodes
III	Local extension of disease into chest wall or mediastinum, heart, or through diaphragm, peritoneum; with or without extrathoracic or contralateral (N3) lymph node involvement
IV	Distant metastatic disease

Note: Butchart stage II and III[15] patients are combined into stage III. Stage I represents resectable patients with negative nodes. Stage II patients are resectable but have positive nodal status. From Sugarbaker DJ, et al. Node status has prognostic significance in the multimodality therapy of diffuse, malignant mesothelioma. *J Clin Oncol.* 1993;11:1172-1178. Reprinted with permission.[12]

Surgery in Trimodality Therapy

Radiotherapy, chemotherapy, and surgery have been used in single- and bi-modality therapy for mesothelioma, but the impact on local control and survival has been poor.[1923] Surgery, as EPP or pleurectomy, may allow palliation.[22,23] Attempts at palliation provided by radiotherapy have been moderately successful at best,[19,20] and the impact of chemotherapy on palliation has been poor. Most single agents are relatively ineffective. A combination of cyclophosphamide, doxorubicin, and cisplatin has provided response rates of 20% to 30%.[21]

The lack of any curative single modality therapy for mesothelioma has led our group and others to evaluate an aggressive trimodal approach to this malignancy. Our current treatment regimen consists of a cytoreductive operation followed by chemotherapy and radiotherapy. This approach maximizes the beneficial effects and minimizes the adverse effects of adjuvant therapy. The two surgical techniques that are currently employed in cytoreduction are pleurectomy/decortication and EPP. These two procedures have not been directly compared in prospective randomized trials. Each surgical technique has advantages and disadvantages. The advantages of pleurectomy/decortication are its low morbidity (25%)[24] and mortality (2%).[18] Thus, this operation can be performed in patients with a less favorable cardiorespiratory status than that required for EPP. However, pleurectomy/decortication may not be feasible if the pleural space is thoroughly obliterated by tumor growth, and the amount of postoperative radiotherapy delivered to the chest cavity is limited due to the presence of the lung parenchyma and the risk of development of postradiation pneumonitis. Furthermore, the local control of disease achieved by

pleurectomy may not be efficient,[25] although the addition of external beam radiation with or without intraoperative brachytherapy may minimize local recurrence. The cytoreduction achieved by the procedure is not as effective as the reduction achieved with EPP. Adequate debulking of tumor in the fissure or near the hilum is also difficult and hazardous.

Some surgeons favor pleurectomy/decortication as the primary procedure for cytoreduction in DMPM. Rusch et al[26] and others added intrapleural chemotherapy with cisplatin and mitomycin postoperatively. At our institute, we attempt to proceed with EPP in all eligible patients and generally perform a pleurectomy only in those patients who are unable to withstand the rigors of EPP.

EPP in the setting of trimodality therapy has several advantages. First, obliteration of the pleural space by tumor does not preclude EPP because the entire pleural envelope is removed en bloc. Also, radiation pneumonitis following surgery is not a concern because the lung has been resected and a higher total radiation dose might be feasible. Most importantly, EPP has been associated with longer than average median survival rates (21 months in some series). However, this apparent benefit could reflect earlier disease stages rather than an effort of the intervention. Currently, the mortality (5%) and morbidity (22%; major complications: 12.5%) are much lower in specialized centers than those reported in the older series.[13,15] Nevertheless, the complication rates following EPP are higher than those following pleurectomy. Another disadvantage of EPP is that the patient must have enough physiologic reserve and adequate cardiac function to tolerate an EPP.

Preoperative Evaluation

The goal of preoperative evaluation is to determine the technical resectability and the ability of the patient to withstand the trimodality therapy. The patient is considered resectable if the tumor is confined to one pleural space without invasion of the mediastinum or any transdiaphragmatic tumor infiltration.

Systematic history is obtained and a physical examination is performed. Premorbid conditions are identified preoperatively because trimodality therapy may worsen any underlying medical condition. We obtain pulmonary function tests, exercise oximetry, arterial blood gas analysis, and occasionally a quantitative ventilation perfusion scan in order to evaluate the respiratory physiological reserve. A 2D ECHO provides a baseline functional evaluation to rule out unsuspected intracardiac abnormalities or pulmonary hypertension as well as baseline cardiac function prior to the adjuvant therapy. A 2D ECHO is also used to screen for pericardial tumor involvement. The physiologic exclusion criteria include ejection fraction of less than 45%, predicted postoperative FEV_1 of less than one liter, inadequate ventilatory function ($Paco_2$ above 45 mm Hg), and Po_2 of less than 65 mm Hg. A chest MRI is obtained to determine the extent of the tumor and to ensure that it is confined to one side only without transdiaphragmatic or mediastinal involvement. If questionable, a laparoscopy or contralateral thoracoscopy with biopsies is performed.

Techniques

Pleurectomy/Decortication

The goal of this procedure is to debulk tumor mass while preserving the underlying normal lung parenchyma. The surgical specimen consists of the parietal pleura and visceral pleura and may or may not include a pericardial or diaphragmatic portion. This operation is performed under general anesthesia and one lung ventilation. Following induction, the patient is placed in the appropriate lateral decubitus

position. A posterolateral thoracotomy is performed followed by a meticulous dissection to remove all gross tumor while preserving the lung. The technical steps of this operation are included in Table 4.

Table 4. – Steps in Operative Technique for Diffuse Malignant Pleural Mesothelioma

Pleurectomy	Extrapleural Pneumonectomy
1. Incision and exposure of parietal pleura	1. Incision and exposure of parietal pleura
2. Dissection of parietal pleura from endothoracic fascia, diaphragm, and mediastinum*	2. Dissection of parietal pleura from endothoracic fascia, diaphragm, and mediastinum*
3. Incision of the parietal pleura and exposure of the visceral pleura	3. Control and division of pulmonary vessels, subcarinal node dissection, staple main stem bronchus
4. Decortication of the visceral pleura	4. En bloc resection of lung, pleura, pericardium, and diaphragm
5. Reconstruction	5. Reconstruction of diaphragm, pericardium**
* May need en bloc resection of diaphragm or pericardium ** In the right side	

The postoperative care centers on analgesia, pulmonary toilet, chest tube care, and ambulation. A pleurectomy may result in some operative blood loss and a large air leak early on. The chest tube output and the air leak usually decrease in the first few postoperative days. Patient-controlled analgesia or, preferably, epidural analgesia is used to control incisional pain. Adequate analgesia facilitates ambulation and pulmonary toilet. Incentive spirometry is important in keeping the lung expanded and avoiding atelectasis. Keeping the lung fully expanded is also necessary to decrease the bleeding from the raw areas. We find that early ambulation is important to both pulmonary toilet and the prevention of deep venous thrombosis. We also routinely use pneumatic compression boots and low-dose subcutaneous heparin to reduce the risk of deep venous thrombosis and pulmonary embolus.

Extrapleural Pneumonectomy

This technique maximizes surgical cytoreduction. The specimen consists of parietal and viscera pleura, pericardial portion, diaphragmatic portion, and the entire lung. The procedure is performed under general anesthesia with double-lumen endotracheal intubation (Table 4). The en bloc resection is accomplished via an extended thoracotomy incision [27] (PLEASE SEE HARD COPY OF JOURNAL FOR FIGURE 2). The diaphragmatic and pericardial defects are repaired with prosthetic patches.

As in the postoperative care described for decortication/pleurectomy, attention is paid to adequate analgesia, pulmonary toilet, strict fluid balance, early ambulation, and deep venous thrombosis prophylaxis. Bronchoscopy is liberally used in clearing thick secretions in patients with poor cough. Close attention to fluid balance is crucial since volume overload can lead to hypoxemia. We recommend fluid restriction to one liter per day in the first three to five days and diuresis as needed to maintain a negative fluid balance and improve oxygen saturation.

Clinical Experience and Results

At our center, patients with mesothelioma are preoperatively evaluated by a multidisciplinary team of clinicians and allied health professionals. Clinical stage, premorbid conditions, resectability, and physiologic status are determined. The inclusion criteria for our preferred trimodality therapy includes adequate cardiac, hepatic, and renal function, sufficient pulmonary reserve to undergo EPP, resectable tumor by radiologic parameters, and Karnofsky performance status greater than 70. Patients undergo an

EPP as the debulking procedure followed by adjuvant chemotherapy and radiotherapy (two cycles of chemotherapy and radiotherapy and concurrent radiotherapy, then two more cycles of chemotherapy). We currently use carboplatin plus paclitaxel for adjuvant chemotherapy. Patients receive two cycles of 200 mg/m^2 of paclitaxel three weeks apart by continuous intravenous infusion (three-hour) and carboplatin AUC (area under the curve) level 6. External beam radiation is then given with concurrent, weekly administration of 60 mg/m^2 of paclitaxel, followed by two cycles of paclitaxel (repeat of initial cycles, 200 mg/m^2 intravenous infusion, three-hour) and carboplatin (AUC level 6). In our original series,[13] the chemotherapy regimen consisted of 50 to 60 mg/m^2 of doxorubicin, 600 mg/m^2 of cyclophosphamide, and 70 mg/m^2 of cisplatin. The change in chemotherapy approach was due to the encouraging preliminary data on carboplatin plus paclitaxel[28] and to avoid cardiac complications from doxorubicin. Radiation is typically given to the entire hemithorax and mediastinum. The borders are the first thoracic vertebral body superiorly, 1.5 cm lateral to the chest wall laterally, approximately 2.5 cm from the edge of the vertebral body to cover the mediastinum medially and 1 cm below the diaphragmatic reflection of the pleura inferiorly (the inferior border is determined by the inferior-most extent of the contralateral intact lung). The hemithorax is treated to 30 Gy in 1.5 daily fractions. If there are localized positive margins or positive lymph nodes, these areas are treated to 2 Gy fractions to a cumulative dose of approximately 54 Gy. The incision and chest tube sites are covered with bolus and included in the treatment field.

A cohort of 120 patients were treated with this trimodality protocol in the period between 1980 to 1995.[13] The morbidity rate was 22%, and the mortality rate was 5%. The survival at two and five years was 45% and 22%, respectively, with 21 months as the overall median survival (PLEASE SEE HARD COPY OF JOURNAL FOR FIGURE 3).[13] A combination of epithelial histology and absence of malignancy in the mediastinal and/or hilar lymph nodes was associated with the best survival outcome. In this particular group (epithelial histology and negative nodes), the two- and five-year survival rates were 74% and 39%, respectively, whereas the subgroup with epithelial tumors and positive lymph nodes had two- and five-year survival rates of 52% and 10%, respectively (PLEASE SEE HARD COPY OF JOURNAL FOR FIGURE 4).[13] Sarcomatous histology was associated with poor prognosis as noted by the two-year survival of 20% and absence of survival at five years (PLEASE SEE HARD COPY OF JOURNAL FOR FIGURE 5).[13] The presence of tumor-involved margins and partial tumor infiltration of the diaphragm did not affect survival. This observation supports our hypothesis that chemoradiation helps in the eradication of the residual microscopic tumor. Survival by stage (Brigham stage) is demonstrated in Fig 1. Survival was 22 months for stage I, 17 months for stage II, and 11 months for stage III.

Conclusions

Mesothelioma is increasing in frequency and presents many diagnostic and management challenges. An optimal universal staging system is still awaiting definition and validation. Prognosis is best for patients with localized disease and epithelial histology. Surgical techniques including pleurectomy/decortication and EPP can result in a major debulking of disease, and studies are ongoing to determine if the addition of chemotherapy and radiation has an impact on survival. Several new investigational approaches are now being tested, including intrapleural interferon gamma, photodynamic therapy, immunotherapy, and gene therapy.

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The Asbestos Alliance
Seeking a Fair Asbestos Solution

Solving the Asbestos Crisis

- History of the Asbestos Issue
- The Scope of the Asbestos Litigation Problem
- How this Crisis Affects You
- Why Congress Must Act
- Proposed Legislative Solution
- Experts Speak Out
- Legislative Update

How to Voice Your Support

The Scope of the Asbestos Litigation Problem

The impact of what Supreme Court Justice David Souter terms the "elephantine mass" of asbestos litigation is vast and far-reaching. Nearly forty years have passed since the first lawsuit was filed, but hundreds of thousands of claims are still pending and new claims are accelerating, especially by those who are not sick. The flood of claims and resulting settlements are forcing companies into bankruptcy and putting at risk compensation for those who are sick today or may become sick in the future. The "elephantine mass {is} still growing" (*Chicago Tribune*, July 22, 2001) and there is no end in sight.

Number of Claims

An estimated 200,000 asbestos claims are pending in state and Federal courts across the country. The total number of claims filed from the onset of asbestos litigation exceeds 555,000 (Credit Suisse First Boston). Filings have increased dramatically, with more than 90,000 in 2001, compared to 20,000 in the early part of the decade. It is estimated that as many as one million claims could be filed before the litigation ends (Tillinghast-Towers Perrin). Who is filing the majority of these claims? "Up to half of asbestos claims are now being filed by people who have little or no physical impairment," said Supreme Court Justice Stephen Breyer. Other experts have estimated that an even higher portion of claims are being filed by those who are not sick.

Costs

So far, companies have paid approximately $20

billion in claims and related costs. Remaining asbestos liability has been estimated at $20 billion to $30 billion by Merrill Lynch and $50 billion by Credit Suisse First Boston. Tillinghast-Towers Perrin has made an even higher estimate, projecting that the total cost of settlements ultimately could reach $200 billion. The weight of the claims and size of settlements have caused or contributed to the bankruptcies of more than 50 companies. Bankruptcies have increased the asbestos liability of the remaining defendants because joint and several liability shifts all of the costs of compensation to these companies, regardless of their actual share of responsibility (Credit Suisse First Boston). The number of asbestos defendants also has risen sharply, from about 300 in the 1980s, to a few thousand today and most are users of the product, not manufacturers (Standard & Poor's). These companies represent at least half of all U.S industries (*RAND*) and include automakers, shipbuilders, textile mills, retailers, insurers, shipbuilders, electric utilities and virtually any company involved in manufacturing or construction in the last thirty years (*Wall Street Journal*).

Impacts

Asbestos leaves many victims in its wake. First and foremost, the sick and their families have suffered. But the flawed asbestos litigation system, which the *Wall Street Journal* terms "The Asbestos Blob," not only hurts the sick and their chance at receiving fair compensation, but also claims other victims. These include employees, retirees and shareholders of affected companies whose jobs, savings and retirement plans are also jeopardized by the tide of asbestos cases. With asbestos litigation affecting so many companies, this also impacts the overall economy due to the trickle-down effects, including jobs, pensions, stock prices, tax revenues and insurance costs.

The Supreme C urt has called f r C ngressi nal acti n on asbest s three

times in the past decade. It's time to heed their call and solve this problem before it's too late.

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In re application of:

Ira Pastan, *et al.*

Application No.: 09/684,599

Filed: October 5, 2000

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After the last line under the "Continuing Data" section, insert --WHICH CLAIMS PRIORITY FROM U.S. PROVISIONAL APPLICATION NO. 60/010,166 FILED 1/05/96--.

Applicants believe no fee is due. In the Preliminary Amendment filed with the above-identified application, the continuing data was correctly stated on page 1. If a fee is due, please charge Deposit Account No. 20-1430 for the fee for a Filing Receipt correction.

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Foreign Applications

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Title

Mesothelin, a differentiation antigen present on mesothelium, mesotheliomas and ovarian cancers and methods and kits for targeting the antigen

Preliminary Class

435